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Small Steps: A Limited ExperimentOpens New ApproachIn Fight Against HIV --- Newly Infected Patients May Squelch Virus Drug-Free, A Boston Study Shows --- Clues From Eight Subjects

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Bruce Walker was a young doctor at Massachusetts General Hospital in the early 1980s when the first patients arrived with what was then a baffling new disease. "I've taken care of patients who've had a lot of false hopes along the way," he says. "I don't want to contribute to that."

But as Dr. Walker, who now also works as an immunology researcher, talks about his new AIDS study, his message contains a sliver of optimism: It may be possible, he says, to "take the immune system and manipulate it to our advantage."

The study, appearing today in the journal Nature, is small, but has potentially big research ramifications. Dr. Walker's team at Massachusetts General has treated a group of very recently-infected HIV patients with drugs -- and then stopped the drugs. With the virus held in check, the immune system developed a vigorous response. In most of the patients, the virus appears to be under control without drugs.

These results, though applicable to only a tiny subsection of AIDS patients, intimates that an HIV vaccine might be possible. The reason is simple: Vaccines also work by stimulating the body's own defenses. The study also encourages an approach to treatment research that until recently has gotten short shrift: fortifying the immune systems of patients infected with HIV, instead of merely trying to subdue the virus.

Researchers have begun flocking to this arena in recent years. They have been spurred in part by the Berlin Patient, a celebrated case that Eric Daar, director of the infectious-disease unit at Cedars-Sinai Hospital in Los Angeles, has dubbed "the most famous anecdote in AIDS science."

In that case, a young German man stopped taking his medicine, against his doctor's advice, and seemed to control his virus. Dr. Walker's team studied the patient's immune system. What they found encouraged Dr. Walker to proceed with the study published today, which was among the first to take patients off drugs.

Nobel laureate David Baltimore, chair of the AIDS Vaccine Research Committee at the National Institutes of Health, says the results were sufficiently "impressive" for him to have revised his testimony before a recent congressional hearing. Dr. Baltimore read an advance copy of the peer-reviewed study, he says, and it helped to change his "public stance about how we are doing in vaccine development. I'm feeling much more optimistic."

The study, however, comes with neon caveats. The subjects in Dr. Walker's study were treated very soon after they contracted HIV -- in most cases, researchers believe, within less than one month. They represent a small fraction of people infected with the virus.

In these lucky few patients, HIV hasn't had time to destroy critical components of the immune system. What Dr. Walker's team apparently did was to preserve defenses these patients still had in place. In patients infected for months or years, researchers face the much harder task of regenerating something lost.

Dr. Walker and Eric Rosenberg, the principal investigator on the study, say they fear that many patients won't make this critical distinction and will stop taking their medications. The method used on the study subjects has so far failed to achieve the same results when tried on patients who have carried the virus in their bodies for months or years.

Another limitation: The patients in the study have been controlling HIV for less than a year. "We cannot yet say what the durability of this effect is," Dr. Walker says. "Our patients know we are considering this a honeymoon period."

Because the study is based on a sample of just eight patients -- without a control group -- it will also have to be replicated by other teams on larger numbers of patients. Such concerns have tempered the reaction of a number of researchers, such as Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases. "It is an advance," Dr. Fauci says. "It is not the answer."

There has long been a cadre of researchers trying to harness the immune system to fight HIV, but this strategy was quixotic as long as there was no way to shield the immune system from the assault of HIV. In 1996, powerful drug cocktails proved capable of suppressing the virus, opening the way for research into complementary therapies that enhance the immune system. "We didn't get to where Walker is today without effective" HIV drugs, says John Mellors, a prominent AIDS researcher at the University of Pittsburgh Medical Center.

Dr. Mellors was skeptical two and a half years ago when he heard about the study. Now he says that it at least "gives a proof of principle to go after. The biggest take-home message is that the human immune system can, under certain circumstances, control HIV infection."

When the drug cocktail first came out, some scientists hoped it would eradicate HIV from the body. But the discovery that HIV can hide for many years in a special kind of cell dashed those hopes -- and intensified interest in supercharging the immune system. Now, numerous trials are testing various strategies, such as experimental HIV vaccines, natural chemicals called cytokines that cause immune-system cells to proliferate, and even gene therapy.

If scientists succeed in transforming such experiments into real-world treatments, patients might escape the side effects that can emerge after years of swallowing the powerful AIDS pills. High cholesterol, changes in body composition, and bone-density problems have been reported. One drug, Glaxo Wellcome's Ziagen, can induce a fatal hypersensitivity reaction in a small proportion of patients. Another, Dupont Pharmaceutical's Sustiva, can cause psychological trouble.

More immediately, the Massachusetts General study could prompt physicians and public health departments to try to identify newly infected people and bring them into care. Treating patients right after they are infected might also help curtail the spread of the disease, as a person is extremely infectious shortly after contracting HIV, when the amount of virus in the blood soars to very high levels.

Of course, the best way to stop the spread of HIV is with a vaccine. Dr. Baltimore believes that the study validates the strategy being pursued by many vaccine developers, including pharmaceutical giant Merck & Co., and the not-for-profit International AIDS Vaccine Initiative.

The vaccines they are testing don't effectively stimulate antibodies -- the traditional goal of vaccines. Instead, they rouse another arm of the immune system called killer T-cells, which destroy HIV-infected cells, much like ranchers who cull sick animals to protect a herd. In most of Dr. Walker's patients, killer T-cells, not antibodies, seem to be controlling HIV. "We've never really been sure of that in people," says Dr. Baltimore, so this study suggests that vaccine research is "on the right track."

Dr. Walker's study builds on research by legions of scientists into the battle between HIV and the immune system. The prevailing theory is that the disease proceeds in the following way. The virus enters the body and is consumed by scavenger cells that shred the virus into fragments. Like scraps of a fugitive's clothing given to bloodhounds, the viral fragments are then presented to immune-system cells including helper T-cells, so named because they "help" the other parts of the immune system mount an effective assault against the virus.

The immune system has billions of helper cells, but each is capable of recognizing only one viral fragment. It is as if each bloodhound could smell only one scent. The helper cells that can recognize a fragment of HIV get activated: They furiously clone themselves to increase their ranks and send out chemical messages that direct the immune system to generate antibodies and deploy the killer T-cells.

This is how the body mobilizes itself against all viral infections. But in the case of HIV, it is committing a suicidal act.

That is because HIV infects helper cells -- especially activated ones. So by the very act of mobilizing a counterattack, the immune system provides HIV with exactly the right cells, in exactly the right state, that it prefers to infect. Worse, the immune system sends to the slaughter its corps of helper cells that are able to orchestrate the body's counteroffensive. Within as little as a few months, most of these critical HIV-specific cells have been killed or damaged, crippling the immune system's ability to defend itself.

Dr. Walker's hypothesis was simple: If doctors could interrupt the battle very early -- after the immune system had met its enemy but before the virus could wipe out helper cells -- then maybe the immune system would be able to develop a strong enough response to gain the upper hand. In essence, Dr. Walker wanted to call a timeout to train the immune system.

Preventive vaccines also train the immune system. Usually made from killed or weakened viruses, vaccines prime the body to be ready with a fully formed defense. So when he was planning his study, Dr. Walker said he wanted to try "vaccinating patients with their own virus."

He was encouraged to go forward when he learned about the Berlin Patient. Months after the Berlin Patient stopped taking his medicine, his immune system was keeping his virus at such low levels that it was undetectable except by a test redesigned specifically to study him. Now, more than three and a half years after he was infected, the amount of HIV in his blood remains extremely low, says his physician, Heiko Jessen.

The Berlin Patient, who doesn't want to be named, believes it was his "will" that suppressed the virus. But when Dr. Walker analyzed his blood, he discovered that he had robust levels of the helper cells that fight HIV -- exactly what his hypothesis predicted. Dr. Walker's study attempted to replicate the experience of the Berlin Patient. Eight patients were treated early in their infection -- in most cases even before antibodies to the virus had developed -- and given a cocktail of HIV drugs. When the researchers stopped the therapy, some patients were able to control HIV right away.

Others needed what amounted to a booster shot. After letting HIV circulate in their bodies for a while, stimulating the immune system, researchers again put these patients on medication, squelching the virus to allow the immune system another chance to catch up. When they stopped therapy a second time, additional patients were able to control the virus without drugs. (Such on-again, off-again therapy is often referred to as "structured-treatment interruption.")

Altogether, five of the eight patients have been controlling their viral load -- a measurement of the amount of HIV in their blood -- below 5,000, and four have usually measured below 500. These are low values. Only about 15% of patients push the virus below 5,000 on their own, and less than 4% get it below 500, according the Multi-Center AIDS Cohort Study, one of the largest and most detailed studies of the natural history of HIV disease.

Still, says Dr. Rosenberg, "we have not cured anyone," a caution Dr. Walker echoes, saying, "We've put them in a kind of remission. We don't know how long that remission will last."

Or even how to induce it in all comers. One patient in the study, who asked not to be identified, tried to manipulate Dr. Walker's theory. After his second time off drugs, his virus hovered around 2,500. To drive the level "even lower," he figured he'd go through a third cycle of start-and-stop therapy. "Well," he says, "the virus didn't cooperate."

He pulls out a hand-drawn graph on which he tracks the amount of virus in his blood. Tracing the line with his finger, he shows how it rose, receded a bit, then climbed back up to more than 13,000. He resumed therapy six months ago and has just elected to try a fourth treatment interruption, which he began last week.

While this patient might have been too sophisticated for his own good, Wilbert Jordan, who founded and runs the Oasis Clinic in South Central Los Angeles, worries about patients at the other extreme. "Half our patients didn't finish high school," says Dr. Jordan. "Some can't read, and many don't speak English as their first language." That makes it hard to communicate the importance of adhering to the standard daily pill-taking schedule, let alone trying to explain more complicated on-again, off-again regimens. He fears the only message patients will hear is that it's okay to stop drugs, undermining their health.

Unless scientists transform today's study into reliable therapy, there will be only a handful of patients like Michael Burns, who participated in Dr. Walker's study. Mr. Burns's immune system suppressed HIV the very first time he went off the drug cocktail. "It's been so liberating," he says, sitting in his backyard with friends for whom he had just thrown a lobster cookout. Mr. Burns, a partner with the accounting firm Grant Thornton in Boston, describes how he disciplined himself to schedule his meals to fit with his demanding HIV regimen. When he stopped taking the pills less than a year ago, he says, "I remember being at the refrigerator at eleven o'clock at night to see what I could eat, simply because I could eat."

The level of HIV in Mr. Burns's blood has been consistently below 500, a very low amount, but he knows his virus could rebound any day. "I'm on a holiday," he says. "I've been given a treat."

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